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Modeling and Simulation of Calcium Dynamics in Fibroblast Cell involving Excess Buffer Approximation (EBA), ER Flux and SERCA Pump

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Abstract

Computational modeling is the use of mathematics and computer science to study the behavior of complex systems by computer simulation. A computational model contains various variables that characterize the system being studied. Simulation is done by adjusting these variables and observing how the changes affect the outcomes predicted by the model. Here, a model has been developed to study complex calcium dynamics in cylindrical shaped fibroblast cell involving three important physiological parameters i.e. EBA (Excess Buffer Approximation) ER (Endoplasmic Reticulum) flux and SERCA (Sacroplasmiel Endoplasmic Reticulum ATPs) pump. The model has been developed for two dimensional unsteady state case along with appropriate initial and boundary conditions according to the physiology of the cell. Finite element technique has been employed to obtain the solution. The cytosol of the fibroblast cell is divided in to 88 elements. A computer programme has been developed in MATLAB 7.10 for the entire problem and the numerical results have been used to study the effect of buffers, ER Flux and source amplitude on calcium distribution in fibroblast cell. This model can be used to study the complex mechanisms of wound repair and tissue remodeling performed by the fibroblast cell.

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Keywords: EBA; Buffers; ER Flux; SERCA Pump; Source Amplitude

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1. Introduction

Computational modeling is an emerging frontier area for research and development in the field of mathematics and computer sciences. Currently available experimental techniques for studying complex dynamic systems do not allow simultaneous studies with many system parameters. However, computational modeling of biological systems[11] makes possible the examination of dynamic system as a whole and the implementations of physiological functions in to artificial systems. Some of the notable examples of these physiological processes are wound healing, tissue remodeling and cell growth. The fibroblast cell plays a crucial role in these processes. These fibroblast cells secrete fibroblast growth factor (FGF), which helps the cell to proliferate[1,2,13] . Another important factor of wound healing is the contraction of fibroblast cell [3]. The calcium plays an important role in triggering the functions and processes of fibroblast. In order to understand the processes of wound healing and tissue remodeling and cell growth, there is a need to understand the calcium dynamics in a fibroblast cell which involves processes like calcium diffusion, calcium buffering, influx, pump, and leak mechanisms etc. Modeling of calcium dynamics in fibroblast poses new challenges for mathematical and computational sciences and therefore it has generated interest among the researchers.The model here presented is built on mathematical and biophysical treatment of parameters obtained from experimental studies of fibroblast cell**.**

Some Experimental investigations are reported in the literature[5,10,16,17] the study of calcium dynamics in fibroblast cell. Also, some attempts are reported in the literature[6,7] for development of one and two dimensional models of calcium diffusion and regulation in presence of time dependent influx for smooth muscle cell to study the magnitude, the spatial and temporal characteristics of calcium transients in restricted diffusion spaces between the plasma membrane and intracellular organelles. But, no attempt is reported in the literature to study the effect of time dependent calcium influx on calcium dynamics in fibroblast cell involving ER flux and plasma membrane transporters with excess buffer approximation. In the view of above, here an attempt has been made to develop a two dimensional model of calcium dynamics in a cylindrical shaped fibroblast cell involving excess buffer approximation along with L-type calcium channel and endoplasmic reticulum based calcium exchange SERCA pump . Finite element method[15] has been used to study the impact of various physiological parameters on calcium dynamics in fibroblast cell. MATLAB program has been developed for graphical representation of these finite element results in two dimensional plots.

2. Mathematical Model

The model cell geometry of fibroblast cell is of cylindrical shape with a maximal diameter[16,17] of 10 μm. The shape was simplified in to cylinder that had a same diameter. The model allows the diffusion along radial and angular direction only. Thus the calcium diffusion in fibroblast cell involving excess buffer approximation with ER flux and SERCA pump (see Fig. 1.) can be rewritten for a two dimensional unsteady state case in polar cylindrical co-ordinates[4] as given below:

$$\frac{\partial [Ca^{2+}]}{\partial t} = D_{Ca}\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial [Ca^{2+}]}{\partial r}\right)+\frac{1}{r}\frac{\partial}{\partial \theta}\left(\frac{1}{r}\frac{\partial [Ca^{2+}]}{\partial \theta}\right)\right) - k_j^{+}[B]_{\infty}\left(\left[Ca^{2+}\right]+\left[Ca^{2+}\right]_{\infty}\right)+$$

$$\frac{A_{ER}}{V_{ER}}K_{IP_3R}\left(\left[Ca_{ER}^{2+}\right]-\left[Ca^{2+}\right]\right)+\frac{A_{ER}}{V_{ER}}\left(\left[Ca_{ER}^{2+}\right]-\left[Ca^{2+}\right]\right)-\frac{A_{ER}}{V_{ER}}\frac{J_{SERCA}^{\max}}{K_{SERCA}}\left[Ca^{2+}\right] \qquad (1)$$

All the parameters and their values are given in table [1].It is assumed that the centre of circle is at (r = 0,θ = 0) and radius of circle is r =5 μm, see Fig 1. The point source is situated at (r = -5,θ = π) and as we move away from the source the calcium concentration in cytosol achieves its background value i.e. 0.1 μM. So the boundary condition takes the following form [8,12,20] :

$$\lim_{\substack{r\to -5\\ \theta\to\pi}}\left(-2\pi r D_{Ca}\frac{\partial[Ca^{2+}]}{\partial r}\right)=\sigma_{Ca} \tag{2}$$

Where σ_{Ca} denotes the time dependent opening and closing of surface membrane Ca channels and it is represented by the following expression[6,7]

$$\sigma_{Ca}=P_0\left(1-\exp\left(-t/T_{on}\right)\right)\left(\exp\left(-t/T_{off}\right)\right) \tag{3}$$

Where P_0 is the permeability constant and T_{on} , T_{off} are time constant. All the parameters were adjusted so that the maximum concentration during the transient matched the current records in the literature[19] .

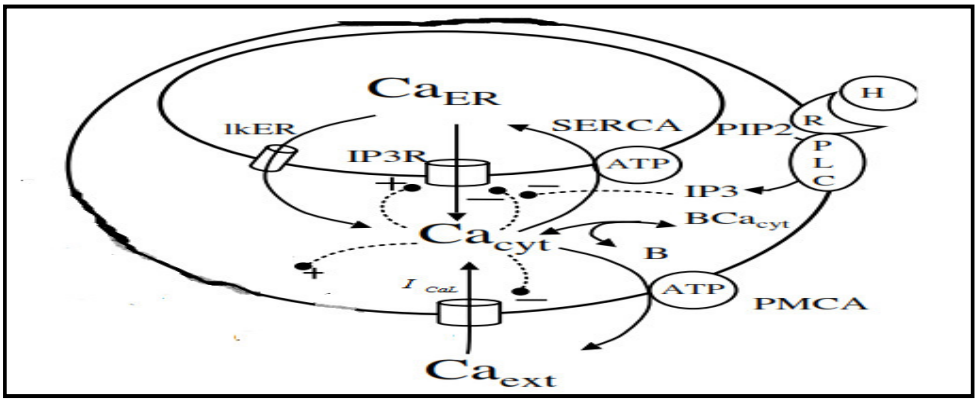

Fig. 1. An overview of complete intracellular calcium dynamics model in fibroblast cell[9]

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For other boundary condition, it is assumed that [Ca^{2+}] attains its steady state concentration 0.1μM as we move far away from the source;

$$\lim_{r\to 5,\theta\to 2\pi}[Ca^{2+}]=[Ca]_{\infty} \tag{4}$$

For our convenience we are writing 'u' in lieu of $[Ca^{2+}]$. Here we are using the finite element method[15], for space discretization (See Fig. 2.) and backward difference method for time derivative.

The discretized variational form[15] of equations (1) to equation (4)

$$I^{(e)}=\frac{1}{2}\int\int_A\left\{r\left(\frac{du^{(e)}}{dr}\right)^2+\frac{1}{r}\left(\frac{du^{(e)}}{d\theta}\right)^2+\frac{1}{D_{Ca}}\left(\eta u^{(e)2}-2\gamma u^{(e)}\right)r+\frac{1}{D_{Ca}}ru^{(e)}\frac{\partial u^{(e)}}{\partial t}\right\}dA-\mu^{(e)}\left(\frac{\sigma_{Ca}}{2\pi D_{Ca}}u^{(e)}\Big|_{r=5}\right) \tag{5}$$

Where 'e' denotes the number of elements i.e. e=1, 2....80. Also the second term (μ (e)=1) for e=40, 50 and (μ (e) =0) for rest of the elements. Here

$$\eta = k_j^+ [B]_\infty + \frac{A_{ER}}{V_{ER}} K_{IP_3R} + \frac{A_{ER}}{V_{ER}} K_{lkER} + \frac{A_{ER}}{V_{ER}} \frac{J_{SERCA}^{\max}}{K_{SERCA}}$$

and $$\gamma = k_j^+ [B]_\infty u_\infty + \frac{A_{ER}}{V_{ER}} K_{IP_3R} u_{ER} + \frac{A_{ER}}{V_{ER}} K_{lkER} u_{ER}$$

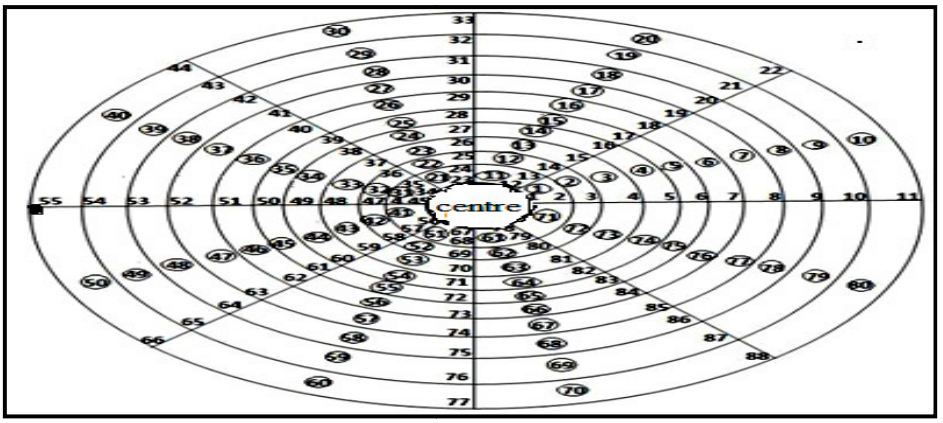

Fig. 2. Finite element discretization of cytosol, here the numbers in circle represents the elements and without circle represents the nodal points and the small dark circle on the left side (at the nodal point 55) represent the point source

The following bilinear shape function for the calcium concentration within each element has been taken as[15] :

$$u^{(e)} = c_1^{(e)} + c_2^{(e)} r + c_3^{(e)} \theta + c_4^{(e)} r\theta \tag{6}$$

$$u^{(e)} = P^T c^{(e)} \tag{7}$$

where, $P^T = [1 \quad r \quad \theta \quad r\theta]$ and $(c^{(e)})^T = [c_1^{(e)} \quad c_2^{(e)} \quad c_3^{(e)} \quad c_4^{(e)}]$ From equation (6) & (7) we get,

$$\overline{u^{(e)}} = P^{(e)} c^{(e)} \tag{8}$$

Where, $\overline{u^{(e)}} = \begin{bmatrix} u_i \\ u_j \\ u_k \\ u_l \end{bmatrix}$ and $P^{(e)} = \begin{bmatrix} 1 & r_i & \theta_i & r_i\theta_i \\ 1 & r_j & \theta_j & r_j\theta_j \\ 1 & r_k & \theta_k & r_k\theta_k \\ 1 & r_l & \theta_l & r_l\theta_l \end{bmatrix}$

From equation (8) we have,

$$c^{(e)} = R^{(e)} \overline{u^{(e)}} \tag{9}$$

where, $R^{(e)} = P^{(e)-1}$

Substituting $c^{(e)}$ from equation (9) in equation (7) we get,

$$u^{(e)} = P^T R^{(e)} \overline{u^{(e)}} \tag{10}$$

Now, the integral $I^{(e)}$ can be in the form

$$I^{(e)} = I_k^{(e)} + I_m^{(e)} + I_\lambda - I_s^{(e)} - I_z^{(e)} \tag{11}$$

Where,

$$I_k^{(e)} = \frac{1}{2}\int_{\theta_i}^{\theta_k}\int_{r_i}^{r_j}\left[r\left(\frac{du^{(e)}}{dr}\right)^2 + \frac{1}{r}\left(\frac{du^{(e)}}{d\theta}\right)^2\right] dr d\theta$$

$$I_m^{(e)} = \frac{1}{2}\int_{\theta_i}^{\theta_k}\int_{r_i}^{r_j}\left[\frac{1}{D_{Ca}}\eta u^{(e)2} r\right] dr d\theta$$

$$I_s^{(e)} = \int_{\theta_i}^{\theta_k}\int_{r_i}^{r_j}\left[\frac{1}{D_{Ca}}\gamma u^{(e)} r\right] dr d\theta$$

$$I_\lambda^{(e)} = \frac{1}{2}\int_{\theta_i}^{\theta_k}\int_{r_i}^{r_j}\left[\frac{1}{D_{Ca}} r\, u^{(e)} \frac{\partial u^{(e)}}{\partial t}\right] dr d\theta$$

$$I_z^{(e)} = \mu^{(e)} \int_{\theta_i}^{\theta_j}\left(\frac{\sigma}{2\pi D_{Ca}} u^{(e)}\,|_{r=5}\right) d\theta$$

Thus, we can write,

$$\frac{dI^{(e)}}{d\overline{u^{(e)}}} = \frac{dI_k^{(e)}}{d\overline{u^{(e)}}} + \frac{dI_m^{(e)}}{d\overline{u^{(e)}}} + \frac{dI_\lambda^{(e)}}{d\overline{u^{(e)}}} - \frac{dI_s^{(e)}}{d\overline{u^{(e)}}} - \frac{dI_z^{(e)}}{d\overline{u^{(e)}}} \tag{12}$$

Using equation (12), we get,

$$\frac{dI}{d\overline{u}} = \sum_{e=1}^{N} \overline{M}^{(e)} \frac{dI^{(e)}}{d\overline{u^{(e)}}} \overline{M}^{(e)T} \tag{13}$$

Where,
$$\overline{M}^{(e)} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ . & . & . & . \\ 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ . & . & . & . \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad I = \sum_{e=1}^{80} I^{(e)} \tag{14}$$

The integral I is extremized with respect to each nodal calcium concentration u_i (i=1, 2.....88). After, rearranging the equations and writing in matrix form, we have a system of ordinary differential equation

$$[K]_{88\times88}[\bar{u}]_{88\times1}+[M]_{88\times1}\left[\frac{d\bar{u}}{dt}\right]_{88\times1}=[F]_{88\times1} \quad (15)$$

Here, $\bar{u}=u_1u_2.....u_{88}$, [K] and [M] are the system matrices and [F] is the system vector. The system (15) is solved using backward difference method. The time taken for simulation is nearly 2 min on aforesaid computer. The numerical results are computed using a programme developed in MATLAB using 7.10 on a intel (R) Core (TM) 2Duo CPU, 4.00 GB RAM,2.00 GHz processor.

3. Results &Discussion

This section shows the results from model simulation of distribution of calcium concentration in two dimensions.To simulate the model of calcium dynamics in fibroblast cell involving the important physiological parameters a MATLAB programe has been developed .The numerical values of physical and physiological parameters used for the computation of numerical results are given in table [1].

Table 1. Values of physiological parameter

Symbol	Parameters	Values	Reference
$[B_\infty]$	Buffer concentration	20 μM	[9]
$\left[Ca^{2+}\right]_\infty$	Background calcium concentration	0.1 μM	Physiological facts
$J_{SERCA}^{\max}$	Maximal pump rate of SERCA	$1.6\times10^{-5}\frac{\mu mol}{(s\times dm^2)}$	[9]
K_{SERCA}	SERCA calcium dissociation constant	0.20 μM	[9]
K_{lkER}	Leak constant	2.0 s^{-1}	[9]
$\left[Ca^{2+}\right]_{ER}$	Endoplasmic reticulum calcium concentration	10.89 μM	[9]
A_{PM}	Plasma membrane area	$2\times10^{-7}\,dm^2$	[9]
A_{ER}	Endoplasmic reticulum area	$0.3\times10^{-7}\,dm^2$	[9]
V_{ER}	Volume of ER	$0.1\times10^{-12}\,dm^3$	[9]
D_{Ca}	Diffusion Coefficient	250μm^2/second	[18]
k_j^+ (EGTA)	Buffer association rate (Exogenous buffer)	1.5μM^{-1} $second^{-1}$	[8,20]

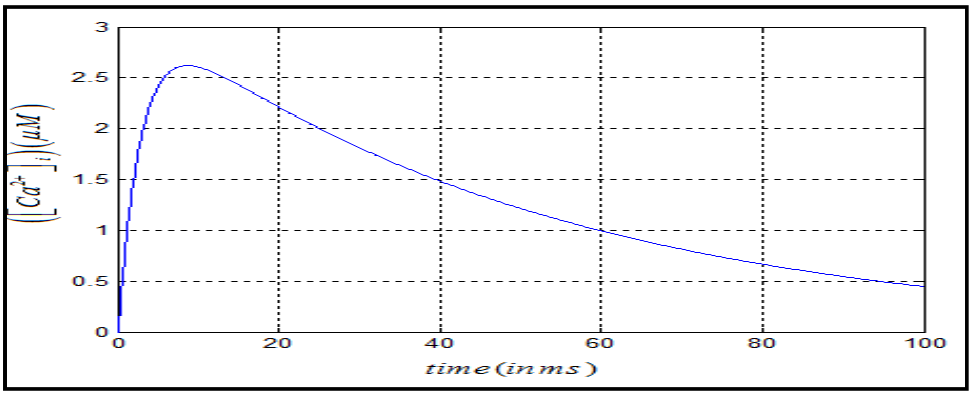

Fig. 3. Calcium concentration profile in fibroblast cell along time at $r = 5\,\mu m, \theta = \pi$

Fig.3 shows the cytosolic calcium concentration with respect to time near open calcium channel. It is observed that initially the cytosolic calcium concentration increases rapidly with time and after that it decreases exponentially till t =100 ms. The maximum calcium concentration is 2.6 μM at t=10 ms in the presence of open calcium channel and closure of calcium channel results the rapid decrease in calcium concentration. The maximum slope is observed in the above fig. between t=20 ms to t =40 ms. The reason behind the sudden fall in cytosolic calcium concentration is the fast activities of calcium buffer near the open channel. After t= 40 ms the calcium concentration decreases gradually and achieves background calcium concentration value after t= 100 ms. Therefore, time dependent calcium influx plays very important role to perform wound healing functions properly in fibroblast cell .

(a) (b) (c)

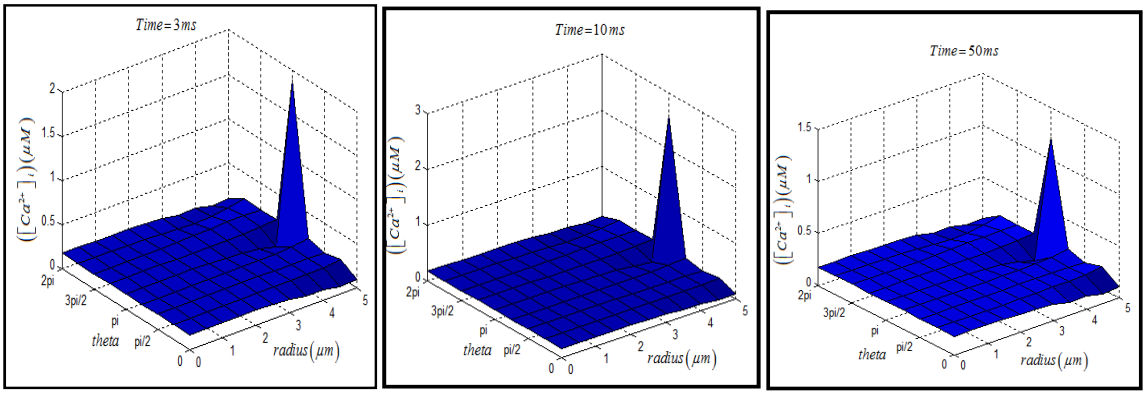

Fig. 4. Spatial calcium concentration profile for time (a) t= 3 ms, (b) t= 10ms (c) t= 50ms

Fig. 4 shows the spatial calcium concentration profile for time t=5ms, t=10ms and t=50ms in the presence of ER flux, L-type calcium channel, and SERCA pump with excess buffer approximation. It is observed from the above

figure that maximum calcium concentration is at $r = 5\,\mu m, \theta = \pi$ *i.e.* near the open channel. The calcium concentration falls sharply after $r = 5\,\mu m$ and achieves background concentration of 0.1 μM . The peak calcium concentration in fig 4(b) is higher than that in fig. 4(a) and 4(c).This is because the activation of time dependent calcium influx at t=10 ms in the above model. While Kargacin et al[7] demonstrated that the calcium concentration near the membrane reaches 2 μM in 20 ms upon the activation of time dependent calcium influx through plasma membrane channel present in smooth muscle cell. It takes longer time period to reach maximum cytosolic calcium concentration in their model because it allows the diffusion in restricted space and our model predicts the free diffusion of calcium in two dimensions not restricted between the plasma membrane and the intracellular organelles.

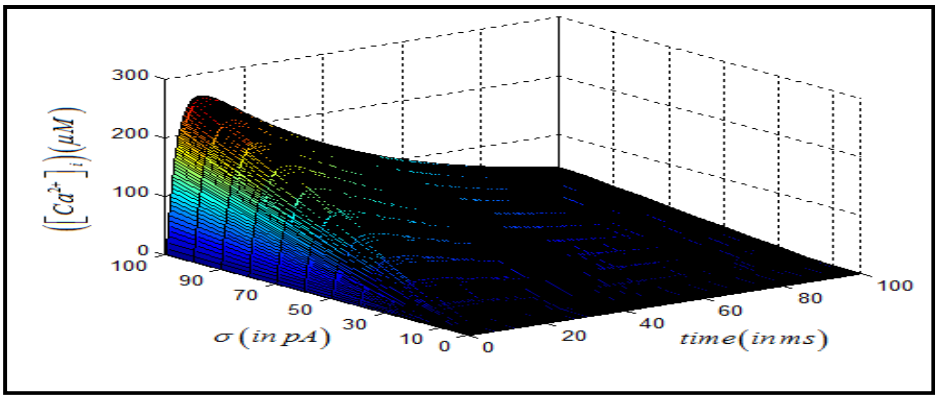

Fig.5. Calcium concentration profile with respect to source amplitude near open calcium channel ($r = 5\,\mu m, \theta = \pi$) and time

Fig. 5 shows the calcium concentration profile near the open Calcium channel. It is observed from the above figure that in the absence of time dependent calcium influx the calcium concentration is at the background calcium concentration i.e. 0.1 μM . Also in the presence of calcium influx as source amplitude increases the calcium concentration in cytosol increases proportionally. This shows that intensity of source amplitude is as important as in the case of constant calcium influx from the plasma membrane channel.

(a) (b)

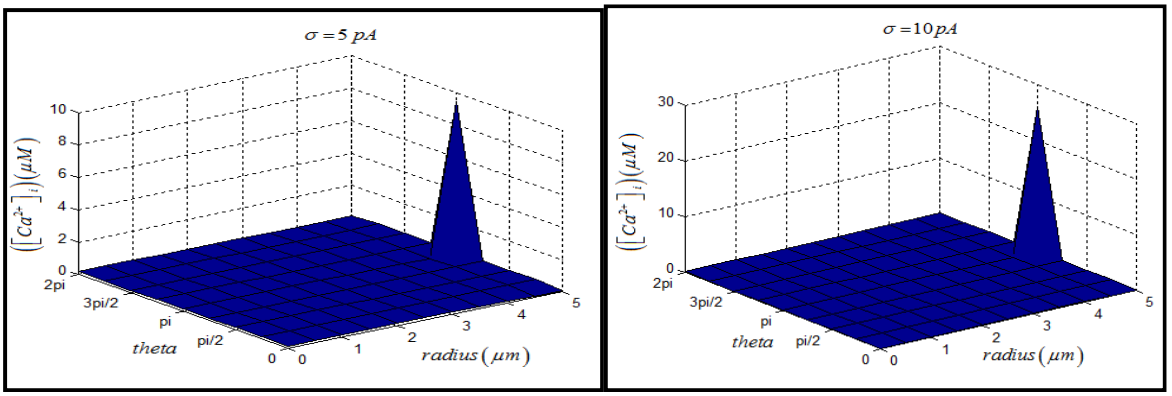

Fig. 6. Spatial calcium concentration profile at t= 10 ms for (a) $\sigma = 5\,pA$, (b) $\sigma = 10\,pA$.

Fig.6 shows the calcium concentration distribution in two dimensions at t =10 ms. It is observed from the Figure that the calcium concentration rises sharply at ($r = 5\,\mu m, \theta = \pi$), when the calcium channel is open near the plasma membrane. It can be concluded from the fig 6 that the maximum calcium concentration in Fig. 6 (b) is almost twice as that of Fig. 6 (a). This implies that the rise in calcium concentration are in the ratio of source amplitude. To evoke an action potential in single NRK fibroblast cell, much higher current pulse is necessary than that in cluster of cells[5]. The present model depicts that 2 pA current is sufficient to evoke action potential in single NRK cell. While this value is quite lower as compared to constant calcium influx of point source and line source[8,14]. Thus, it concluded that the calcium concentration increases proportionally for increasing values of source amplitude irrespective of time dependent calcium influx or time dependent calcium influx.

4. CONCLUSION

Coaxial circular sector based finite element approach was developed and employed to study calcium diffusion for two dimensional cases in a fibroblast cell in this model. This approach gives us comparably good approximation of the complex geometry of the cell including various biophysical parameters like ER flux, receptors, Pumps, leak and Plasma membrane calcium channels. These models were employed to study various physiological processes in cell. The study of time dependent calcium influx on calcium dynamics performed by using the finite element method gives us new insight of the calcium patterns in a fibroblast cell. Such models can be further developed to get better insight of Spatio-temporal calcium concentration patterns in fibroblast cell under various normal and abnormal conditions. The information generated from these models may of great use to biomedical scientists for understanding the structure and processes of fibroblast cells in wound healing, tissue remodeling and growth.

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